UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/890,112	12/26/2001	Andre Rosowsky	48460(70157)	5913

21874 7590 04/29/2004

EDWARDS & ANGELL, LLP
P.O. BOX 55874
BOSTON, MA 02205

EXAMINER	
MCKENZIE, THOMAS C	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 04/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/890,112	ROSOWSKY, ANDRE	
	Examiner	Art Unit	
	Thomas McKenzie, Ph.D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-12,14-26 and 28-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1,3,4,6,7 and 10* is/are allowed.

6)☒ Claim(s) *5,11-25 and 28-34* is/are rejected.

7)☒ Claim(s) *8,9 and 26* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to amendments filed on 2/17/04. Applicant has amended claims 1, 5-7, 11, 12, 18-21, and 26. Applicant has canceled claims 13 and 27. There are thirty-one claims pending and under consideration. Claims 1 and 3-10 are compound claims. Claim 26 is a composition claim. Claims 11, 12, 14, 15, and 28-34 are use claims. This is the third action on the merits. The application concerns some dibenazepine compounds, compositions, and uses thereof.

2. In the previous office action, the Examiner failed to include claim 34 in the blanket rejection concerning enablement for prevention. That error is presently corrected and for that reason alone, the present action is made non-Final.

Response to Amendment

3. Applicant has declined to follow the suggestion made in point #3 of the previous office action and the request is withdrawn. Applicant's amendment overcomes the objection made in point #4. The deletion of about overcomes the indefiniteness rejection made in point #5.

Claim Rejections - 35 USC § 112

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Claim 5 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Variables T, U, and V may be "optionally substituted nitrogen", yet in Formula III all three atoms have three required bonds. Nitrogen is a trivalent atom. In a six-membered ring it is not chemically possible for a nitrogen atom to have an external substituent.

The Examiner suggests removing "optionally substituted" concerning nitrogen.

Applicant makes two arguments. Firstly, that the orthogonal p_z' hybridized nitrogen orbital on atoms T, V, and V, which is filled with a pair of electrons from the nitrogen atom, "can form covalent bonds with hydrogen or hydrocarbon fragments to form an ammonium salt which comprises four covalent bonds to nitrogen." Secondly, that "[c]laim 5 provides compounds of Formula III and pharmaceutically acceptable salts thereof. One skilled in the art will understand that pharmaceutically acceptable salts of compounds of Formula III comprise at least one protonated nitrogen or amino residue or at least one substituted nitrogen at one of the T, U, or V positions and a pharmaceutically acceptable anion notwithstanding the absence of an indication of a charge in the structure of Formula III."

This is not persuasive. Firstly, the plain meaning of "substituted" is that one object is replaced by another. In a chemical context, this means that some other

univalent radical replaces a hydrogen atom. Both the N-oxide and the N-alkyl pyridinium salts, of which Applicants allude, are not formed by removing anything from the complete formula of molecule III. Both the N-oxide and the N-alkyl pyridinium salts are conceptually formed by simple addition of an oxygen atom from an oxidizing agent or a simple addition of an alkyl radical from an alkylating agent. There is no substitution going on in either process. There is no support in the specification for N-oxides or N-alkyl pyridinium salts of any sort.

Secondly, N-alkyl pyridinium salts are not "pharmaceutically acceptable". It even stretches the meaning of the word salt to call them salts. A salt is the reaction product of a base and an acid. A proton is transferred during salt formation. An alkyl group is transferred during the formation of N-alkyl pyridinium salts.

5. Claims 11, 12, 14-25, and 28-33 remain rejected and claim 34 is newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating patients suffering from diseases, does not reasonably provide enablement for treating patients "susceptible to a" disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The only established prophylactics are vaccines not the dibenazepine compounds such as present here. It is presumed that prevention of

the claimed diseases would require a method of identifying those individuals who will develop the claimed diseases before they exhibit symptoms. There is no evidence of record that would guide the skilled clinician to identify those who have the potential of becoming afflicted. All people are susceptible to parasitic diseases.

"The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art, and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. 1) As discussed above, preventing diseases requires identifying those patients who will acquire the disease before parasitic infection occurs. This would require extensive and potentially opened ended clinical research on healthy subjects. 2) The paragraph spanning page 16 to page 17 lists the diseases Applicant intend to treat. In the final two sentences there is a discussion of AIDS and cancer patients. Are these the only patients "susceptible to a" infection, or are there others? 3) There is no working example of such a preventive procedure in man or animal in the specification. 4) The claims rejected are drawn to clinical infective medicine and are therefore physiological in nature. 5) The state of the art

is that no general procedure is art-recognized for determining which patients generally will become infected by parasites before the fact. Despite intensive efforts, pharmaceutical science has been unable to find a way of getting a compound to be effective for the prevention of parasitic diseases generally. Under such circumstances, it is proper for the PTO to require evidence that such an unprecedented feat has actually been accomplished, *In re Ferens*, 163 USPQ 609. No such evidence has been presented in this case. 6) The artisan using Applicants invention would be a Board Certified physician in infectious diseases or tropical medicine with an MD degree and several years of experience. The failure of skilled scientists to achieve the goal of preventing all parasitic infections is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs. Novo Nordisk*, 42 USPQ2nd 1001, 1006. This establishes that it is not reasonable to any agent to be able to prevent infections by parasites generally. That is, the skill is so low that no compound effective generally against parasitic disorders has ever been found let alone one that can prevent such conditions. 7) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). 8) The claims broadly read on all

patients, not just those undergoing therapy for the claimed diseases. The term parasitic disease is a general category that arises from dissimilar organisms related only by a shared behavior. This is a very diverse set of creatures with nothing in common biochemically or morphologically. Most of these parasites do not rely upon the dihydrofolate reductase enzyme which is found in malaria parasites and which is described in the *in vitro* assay in lines 4-12, page 37 of the specification. Even if Applicant's compounds could prevent malaria, there is no reason to believe that infection by other parasites lacking this enzyme could be prevented. Additionally, the claims read on the multitude of compounds embraced by Formula I. Thus, the claims are extremely broad.

The Examiner suggests deletion of the phrase "susceptible to a".

Applicant has added a phrase limiting the methods to treatment of immunosuppressed patients and offer AIDS patients and those undergoing immunosuppressive cancer treatment as examples of such patients. This is unpersuasive for two reasons. Firstly, the breadth of parasitic infection is broad and it is unclear that even cancer patients, for example, are universally susceptible to all parasites. Secondly, only claims 15-17, 29, and 30 are limited to AIDS and cancer patients. The features upon which applicant relies (i.e., AIDS and cancer) are not recited in rejected claims 11, 12, 14, 18-25, 28, and 31-34. Although the

claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Allowable Subject Matter

6. Claims 1, 3, 4, 7, and 10 are allowed. Claims 8, 9, and 26 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

7. Information regarding the status of an application should be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free). Please direct general inquiries to the receptionist whose telephone number is (703) 308-1235.

8. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose

telephone number is (571) 272-0670. The FAX number for amendments is (703) 872-9306. The PTO presently encourages all applicants to communicate by FAX. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, please contact James O. Wilson, acting SPE of Art Unit 1624, at (571)-272-0661.

Thomas C. McKenzie, Ph.D.
Patent Examiner
Art Unit 1624

TCMcK/me